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Part V

Environmental Protection Agency

Interagency Testing Committee; Receipt of Fourth Report and Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[OTS-410001; FRL 1237-1]

Fourth Report of the Interagency Testing Committee; Receipt of the Report and Request for Comments

AGENCY: Environmental Protection Agency (EPA).

ACTION: This Notice requests comments on recent additions to the Interagency Testing Committee's (ITC) priority list of chemical substances recommended for testing under section 4(a) of the Toxic Substances Control Act (TSCA). In addition, a change in ITC procedure for transmitting dossiers of support information is described.

SUMMARY: The ITC, established under section 4(e) of TSCA, has transmitted its Fourth Report to the Administrator of EPA. This report revises and updates the Committee's Priority List of chemicals. The Report identifies those additional chemical substances the Committee is recommending to EPA for priority consideration for promulgation of test rules under section 4(a) of the Act.

The Fourth Report is being published with this Notice. The Agency invites interested persons to submit comments on the Report.

SUPPLEMENTARY INFORMATION:

Background

Section 4(a) of TSCA authorizes the Administrator of EPA to promulgate regulations requiring testing of chemical substances in order to develop data relevant to determining the risks that such chemical substances may present to health and the environment.

Section 4(e) of TSCA established an Interagency Testing Committee to make recommendations of chemical substances to the Administrator of EPA to be given priority consideration for proposing test rules under section 4(a). The Committee may at any one time designate up to 50 of its recommendations for special priority consideration by EPA. Within 12 months of that designation, EPA must initiate rulemaking to require testing or publish in the **Federal Register** its reasons for not doing so.

The Committee's initial recommendations to the Priority List, of four substances and six categories of substances, were published in the **Federal Register** on October 12, 1977 (42 FR 55026). EPA's response to the initial recommendations appeared in the **Federal Register** on October 26, 1978 (43 FR 50134). The ITC's revisions to the initial list appeared in the Committee's Second Report and were published in the **Federal Register** on April 19, 1978 (43 FR 16684). Those revisions were the addition of four substances and four categories of substances to the Priority List. EPA's response to the second ITC Report was signed by the Deputy Administrator of EPA on May 8, 1979 (see 44 FR 28095, May 14, 1979). In its Third Report, published in the **Federal Register** on October 30, 1978 (43 FR 50631), the Committee recommended the addition of one chemical substance and two categories of chemical substances to the Priority List. Subsequently, on March 29, 1979, the Agency published a Notice of a correction made by the ITC in the material under the heading "Carcinogenicity" and a definition of the term "derivatives" as it appears for the category "Glycidol and Its Derivatives" (43 FR 18733).

In this Fourth Report, the Committee is recommending the addition of 11 individual chemicals and one category to its Priority List. Each of these new recommendations has been designated by the Committee for priority consideration by EPA. The format of this Report differs from that of the earlier reports. In the past, the Committee presented summary rationales for its recommendations in the Report to the Administrator and provided separate dossiers of support information that were transmitted to EPA following the Agency's receipt of a Report. The heading "Reasons for Recommendations" now appears in the Report for each designated substance. This rationale section presents the Committee's review of information from the scientific literature and other sources used to arrive at the ITC designations. No separate dossiers will be forwarded to EPA by the Committee.

Availability

The ITC's Fourth Report appears following this Notice.

Request for Comments

EPA invites interested persons to submit comments on the Committee's new recommendations. The Agency requests that comments be submitted no later than July 31, 1979. All comments received by that date will be considered by the Agency in determining whether to propose test rules in response to the Committee's new recommendations.

Comments should bear the identifying notation OTS-410001 and should be submitted to the Document Control Officer, Chemical Information Division, Office of Toxic Substances (TS-793), Room 447, EPA, 401 M Street SW., Washington, D.C. 20460. All written comments will be available for public inspection in Room 447, East Tower, at the same address, between 8:30 a.m. and 4:30 p.m., weekdays.

Dated: May 18, 1979.

Steven D. Jellinek,

Assistant Administrator for Toxic Substances.

Toxic Substances Control Act, Interagency Testing Committee.

Honorable Douglas M. Costle,

Administrator, Environmental Protection Agency (A-100), Room 1200 W, 401 M Street, SW., Washington, D.C. 20460.

Dear Mr. Costle: On behalf of the TSCA Interagency Testing Committee, I am transmitting to you the Committee's Fourth Report. This Report revises the Section 4(e) Priority list with the addition and designation of eleven individual chemicals and one category.

You will note that the format of this Report differs from earlier reports in that the Committee's recommendations and reasons for recommendations are contained in rationales on the designated substances. Dossiers of supporting information will not be transmitted separately, as the rationales contain the key information from the scientific literature and other sources used by the Committee in making its decisions on the designations. The Committee hopes that this new format provides a more timely presentation of relevant information than our previous practice of sending dossiers to you several months after the report.

During the past six months, the Office of Toxic Substances has increased the level of staff support to the Committee. This has aided us in our work and is greatly appreciated.

Sincerely yours,

Carter Schuth,

Chairperson, TSCA Interagency Testing Committee.

Fourth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency

April 1979.

Summary

A major section (Sec. 4) of the Toxic Substances Control Act of 1976 (TSCA, Pub. L. 94-469) provides for the testing of chemicals in commerce which may pose an unreasonable risk to human health or the environment. This section of the Act also provides for establishment of a Committee, composed of representatives from eight designated Federal agencies, to recommend chemical substances or mixtures to which the Administrator of the U.S. Environmental Protection Agency (EPA) should give priority consideration for the promulgation of testing rules. The Committee makes

such revisions in the Section 4(e) Priority List as it determines to be necessary and transmits them to the Administrator, at least every six months.

As a result of its deliberations during the past six months, the Committee is revising the TSCA Section 4(e) Priority List by the addition of eleven individual substances and one category all designated for action by EPA within twelve months. The Committee considers each newly designated addition to be equal priority with those previously designated. The additions to the Priority List are presented alphabetically, together with the types of studies recommended, as follows:

Substances and categories designated	Recommended studies
Acetonitrile	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Epidemiology
Aniline and Chloro-, Bromo-, and/or Nitro-Anilines.	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Environmental Effects, Epidemiology
Antimony	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Environmental Effects, Epidemiology
Antimony Sulfide	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Environmental Effects, Epidemiology
Antimony Tnoxide	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Environmental Effects, Epidemiology
Cyclohexanone	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Environmental Effects, Epidemiology
Hexachlorocyclo-pentadiene.	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Environmental Effects
Isophorone	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Epidemiology
Mesityl oxide	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Epidemiology
4,4'-Methylenedianline	Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Effects, Environmental Effects, Epidemiology
Methyl ethyl ketone	Chronic Effects, Epidemiology
Methyl isobutyl ketone	Mutagenicity, Teratogenicity, Chronic Effects, Epidemiology.

TSCA Interagency Testing Committee

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* Dr. Bates replaced Dr. Falk as member on April 1, 1979.

Acknowledgments

The Committee members acknowledge the support and invaluable contributions of the many individuals and groups who have significantly aided us in preparing this report. These include:

The Federal agencies who have cooperated by providing support through the liaison members;

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John W. Lyon, Office of General Counsel
Ralph C. Northrop, Jr., Office of Toxic Substances
Amy Rispin, Office of Toxic Substances
Justine Welch, Office of Toxic Substances
Ronald Stanley, Office of Toxic Substances
David Lynch, Office of Toxic Substances

The numerous experts who prepared presentations and material for the Committee;

The industries that responded to the Contractor's request for information on specific chemical substances and categories; and

The many individuals and organizations who responded to the Committee's previous reports.

**Until March 24, 1979.
***Commencing April 2, 1979.

Fourth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency, April 1979

Chapter 1. Introduction

1.1 *Background*

The Interagency Testing Committee (Committee) was established under Section4(e) of the Toxic Substances Control Act of 1976 (TSCA, P.L. 94–469). The specific mandate of the Committee is to identify and recommend to the Administrator of the U.S. Environmental Protection Agency (EPA) chemical substances or mixtures in commerce which should be tested to determine their potential hazard to human health and/or the environment. The Act specifies that the Committee's recommendations to the Administrator will be in the form of a list [Section 4(e) Priority List] to be published in the **Federal Register.** The Committee also is directed to make such revisions in the list as it determines to be necessary and transmit them to the Administrator, at least every six months after submission of its initial list.

The current Committee members, alternates, and liaison representatives are identified in the front of this report. The Committee's chemical review procedures and previous reports have been detailed elsewhere (Reference Nos. 1–4) and are not reiterated herein.

1.2 *Committee Activities in this Reporting Period*

During the past six months, the Committee has completed a review of all chemical substances and categories on its Preliminary List (Reference No. 1), with the exception of some chemicals whose consideration has been deferred pending receipt of additional information. The Committee has initiated several actions in an attempt to obtain the information necessary for evaluation of deferred chemicals. These actions include having the Committee's technical support contractor directly request production, use and other available data from chemical manufacturers; requesting of the EPA Administrator that the Committee have access to the TSCA Inventory data; and requesting that the Administrator assist the Committee in obtaining information through TSCA Section 8(a) or by other appropriate means.

The Committee has also completed an update of its master file of chemicals and has scored exposure and biological activity of chemicals selected from the master file (see Reference No. 2 for methodology). This update has included incorporating the most recently available version of some of the source

lists, e.g., government sponsored data bases, and scoring the exposure potential for chemicals whose production volumes were not previously available. A number of these newly scored chemicals and others to be selected during the next six months will be reviewed in detail for the purpose of making future recommendations to the EPA Administrator.

Other activities since the last report include a Committee initiated review of its chemical scoring system through a workshop (February 25–28, 1979). Approximately one-hundred invited experts from academia, industry, public interest groups and government were asked to critically evaluate and make recommendations for improving the current chemical scoring system. Workshop participants, selected on the basis of their knowledge on scoring systems or components thereof, accomplished their task through a series of plenary and concurrent working sessions devoted to specific factors which compose the overall scoring system. A report of the workshop (to be available in late summer 1979) will be used by the Committee to determine if changes are needed in its chemical scoring system.

In order to accomplish its work in a more timely fashion, the Committee has initiated some changes in the format for reporting to the Administrator. In place of dossiers of supporting material which were forwarded to the Administrator following each of the previous reports, the fourth report contains rationales, which are found in Section 2.2. Each of these rationales contains a brief description of the physical and chemical characteristics of the chemical, selected information from the scientific literature and from government reports, the Committee's recommendations concerning specific effects of concern and a bibliography. In some instances listing of background references is provided in addition to those cited in the rationale.

In contrast to the dossiers, the rationales do not contain reference to planned or ongoing studies, although the Committee may be aware of such studies. In this regard, the Committee's reasoning in the present or future designation of substances on which studies are planned or ongoing remains the same as stated and explained in Section 3.2 of the Third Report (4): "The Committee generally does not regard knowledge that studies are planned or ongoing as a sufficient basis to defer consideration of a substance for designation for the effect under investigation or for any other effect. The Committees judgment as to whether a substance has been adequately tested for health and environmental effects must rest with the data that are presently available. Such data do not exist for planned studies and may be in various stages of generation for ongoing studies."

1.3 *EPA's Response to the Committee's First Report*

In this Report, several chemical substances and categories appear on the Section 4(e) Priority List with designations for action by October 1978. These chemicals were designated for action by the Administrator in the Committee's First Report in October 1977. As announced in the Federal Register (43 FR 50134–50138, October 26, 1978), EPA has initiated review and evaluation of these initial recommendations. These chemicals are still retained on the Section 4(e) Priority List as shown in Table 1.

Chapter 2. Recommendations of the Committee

2.1 *Chemical Substances Designated for Action by EPA Within Twelve Months*

The Committee is revising its TSCA Section 4(e) Priority List by the addition of eleven individual substances and one category for which initiation of testing rules is recommended. These chemicals were selected after consideration of: the factors identified in TSCA Section 4(e)(1)(A), including the reasonably foreseeable availability of facilities and personnel for performing the recommended tests (see Reference Nos. 3–4 for detailed discussion); other relevant factors identified by the Committee; and the knowledge and professional judgment of Committee members. The recommended studies deemed appropriate for determining the potential hazard(s) of each new entry and the reasons for such recommendations are described in Section 2.2 of this report and summarized in Table 2. As in the case of the Committee's previous recommendations, these chemical substances are being designated by the Committee for action by EPA within twelve months. The Committee assigns equal priority to all newly designated entries. Therefore, each of the new entries should be given the same priority for purposes of initiating action under TSCA Section 4(a).

Unless stated otherwise, the chemical substance recommended for toxicological testing is the product to which the population is exposed. In some cases, the Committee has refrained from recommending environmental effects studies because information concerning the fate of the chemical is insufficient to establish whether significant environmental concentrations are likely to occur. Where testing for environmental effects is recommended the appropriate tests will depend on the predicted environmental fate of the chemical in question. Information available to the Committee generally does not permit recommendation of specific effects tests, or tests on particular indicator organisms for specific ecosystems. Therefore, while specific health effects tests can be recommended, the recommendation to perform environmental effects testing must necessarily remain general.

Where epidemiological studies are recommended the Committee has not determined if the appropriate cohorts can be identified.

Antimony, antimony sulfide and antimony trioxide are being listed separately, (see Table 1); but one rationale in Section 2.2 contains the Committee's recommendations and reasons for designation for all three chemicals.

Table 1. *The TSCA Section 4(e) Priority List.*

	Designated for action by: *
Acetonitrile	April 1980
Acrylamide	April 1979
Alkyl epoxides	(October 1978)
Alkyl phthalates	(October 1978)
Aniline and bromo, chloro, and/or nitroanilines	April 1980
Antimony (metal)	April 1980
Antimony sulfide	April 1980
Antimony trioxide	April 1980
Aryl phosphates	April 1979
Chlorinated benzenes, mono- and di-	(October 1978)
Chlorinated benzenes, tri-, tetra- and penta-	October 1979
Chlorinated naphthalenes	April 1979
Chlorinated paraffins	(October 1978)
Chloromethane	(October 1978)
Cresols	(October 1978)
Dichloromethane	April 1979
1,2-Dichloropropane	October 1979
Cyclohexanone	April 1980
Glycidol and its derivatives	October 1979
Halogenated alkyl epoxides	April 1979
Hexachloro-1,3-butadiene	(October 1978)
Hexachlorocyclopentadiene	April 1980
Isophorone	April 1980
Mesityl oxide	April 1980
4,4'-Methylenedianiline	April 1980
Methyl ethyl ketone	April 1980
Methyl isobutyl ketone	April 1980
Nitrobenzene	(October 1978)
Polychlorinated terphenyls	April 1979
Pyridine	April 1979
Toluene	(October 1978)
1,1,1-Trichloroethane	April 1979
Xylenes	(October 1978)

*Chemicals followed by dates in parenthesis were designated by the Committee (Ref. 2) and responded to by the Administrator in 43 FR 50134–50138.

Table II.—*Summary of Studies Recommended in This Report*

Substance or category	Carcinogenicity	Mutagenicity	Teratogenicity	Chronic effects	Environmental effects	Epidemiology
Acetonitrile	×	×	×	×		×
Aniline and Bromo: Chloro, and/or Nitroaniline	×	×	×	[a,b] ×	×	×
Antimony	×	×	×	[f] ×	×	×
Antimony Sulfide	×	×	×	[f] ×	×	×
Antimony Trioxide	×	×	×	[f] ×	×	×
Cyclohexanone	×	×	[b] ×	[a,f] ×	×	×
Hexachlorocyclopentadiene	×	×	×	[a,b] ×	×	×
Isophorone	×	×	×	[a,b] ×		×
Mesityl Oxide	×	×	×	[b] ×		×
4,4'=Methylenedianiline	×	×	×		×	×
Methyl Ethyl Ketone				[a] ×		×
Methyl Isobutyl Ketone		×	×	×		×

[a] With emphasis on neurological effects.
[f] With emphasis on reproductive effects.
[b] Including behavioral effects in offspring.
[h] With emphasis on hematopoietic effects.

References

1. Preliminary List of Chemical Substances for Further Evaluation, Toxic Substances Control Act Interagency Testing Committee, July 1977.

2. Initial Report to the Administrator, Environmental Protection Agency, TSCA Interagency Testing Committee, October 1, 1977. Published in the Federal Register, Vol. 42, No. 197, Wednesday, October 12, 1977, pp. 55026–55080. The report and supporting dossiers also were published by the Environmental Protection Agency, EPA 560–10–78/001, January 1978.

3. Second Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency, TSCA Interagency Testing Committee, April 1978. Published in the **Federal Register**, Vol. 43, No. 76, Wednesday, April 19, 1978, pp. 16684–16688. The report and supporting dossiers also were published by the Environmental Protection Agency, EPA 560–10–78/002, July 1978.

4. Third Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency, TSCA Interagency Testing Committee, October 1978. Published in the **Federal Register**, Vol. 43, No. 210, Monday, October 30, 1978, pp. 50630–50635.

2.2 *Rationales*

Acetonitrile

Recommended Studies:
Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Epidemiology

Physical and Chemical Information:
CAS No. 75–05–8
Structural Formula: $H_3C\text{-}C\equiv N$
Empirical Formula: C_2H_3N
Molecular Weight: 41.05
Boiling Point: 81.6° C
Vapor Pressure: 100 mm @ 27°C
Log Partition Coefficient: −0.34

Acetonitrile is a polar solvent with a high dielectric constant. It is miscible with water, methanol, ethanol, carbon tetrachloride, acetamide, ethyl acetate, ethylene dichloride, ethyl ether, and acetone.

Reasons for Recommendations

Production, Release, and Exposure: Acetonitrile is produced as a by-product during the synthesis of acrylonitrile. This synthetic process known as the SOHIO process involves the high temperature catalytic reaction between propylene and ammonia (Stobaugh et al., 1971). The SOHIO process is the principal route to both acrylonitrile and acetonitrile which is produced at the rate of 0.035 lb/lb of acrylonitrile (Lowenheim and Moran, 1975). The production volume for acetonitrile for 1977 has been given as 57.8 million pounds (ITC, 1977). Since the growth rate of acrylonitrile is projected at 6 to 8% for the next five years, 1982 production of acetonitrile could range between 77 to 85 million pounds (Anon., 1975).

Commercially, acetonitrile finds its greatest use as a volatile solvent and as an extracting fluid for fatty acids, animal and vegetable oils, fish liver oils, and unsaturated petroleum hydrocarbons (Hawley, 1971). In addition, acetonitrile is a starting material in the synthesis of specialty chemicals such as acetophenone, alpha-naphthalene acetic acid, thiamine, and acetamidine (Hawley, 1971).

The greatest potential for exposure to acetonitrile occurs in the workplace. Synthesis of acetonitrile is carried out in a closed system so that exposure would occur as the result of accidental escapes during production, transfer and storage. Since much of the chemical has noncaptive uses, such as an extracting solvent, many more people could be exposed besides those engaged in synthesis operations. Exposure could occur via inhalation or absorption though the skin (Fassett, 1963). NIOSH estimates that 23,000 workers may be exposed to acetonitrile (NIOSH, 1979).

Effects of Concern

Carcinogenicity

No studies were found in the searched literature which could be used in assessing the carcinogenic potential of acetonitrile. In rabbits, thyroid hyperplasia and resulting abnormal protrustion of the eyeball was observed after 14 to 60 days of daily intramuscular injection of 0.05–0.1 ml of acetonitrile (Marine et al., 1933). As discussed below, a wide range of tissue changes has been observed in rats, monkeys, dogs and humans after exposures ranging from single doses to ninety daily doses. Because of the short duration of the reported studies, none is adequate to establish the carcinogenic potential of acetonitrile. Possible contamination of acetonitrile by acrylonitrile, a carcingen (NIOSH, 1978a), should be investigated. Because of the wide range of degenerative tissue changes observed even in these studies of short duration, the Committee recommends that acetonitrile be tested for carcinogenic potential.

Mutagenicity

No studies on the possible mutagenicity of acetonitrile were found in the searched literature. The Committee recommends that acetonitrile be tested for mutagenicity.

Teratogenicity

No studies on the possible teratogenicity of acetonitrile were found in the searched literature. The Committee recommends that acetonitrile be tested for teratogenicity.

Chronic Effects

The metabolism and pharmacokinetics of acetonitrile presents a complicated picture. In all species studies to date (rat, monkey, dog, human), great individual differences have been observed; and generalizations are tenuous regarding the fate of acetonitrile in mammals and humans. The major toxic effects of exposure to acetonitrile apparently result from the produciton of hydrogen cyanide which then acts to inhibit

cytochrome oxidase, thus impairing cellular respiration. This hypothesis is supported by the work of Lang (1894, as cited in Pozzani et al., 1959) who reported that formate and cyanide are the metabolic products of acetonitrile in dogs. Giacosa (1883, as cited in Pozzani et al., 1959) reported the metabolites as acetic acid and ammonia. The formation of cyanide in mammals and humans after acetonitrile exposure is supported by the autopsy reports of two human poisoning victims which showed high levels of cyanide in various organs, blood and urine (Amdur, 1959; Dequidt et al., 1974) and by studies in rats, monkeys and dogs showing urinary thiocyanate in all three species after inhalation of acetonitrile and free cyanide in the blood of the monkeys and dogs (Pozzani et al., 1959). After intraperitoneal (i.p.) injection of acetonitrile, rats excreted acetonitrile, and free and conjugated hydrogen cyanide in the urine. After lethal i.p. doses to rats, acetonitrile and free and conjugated cyanide were found in various organs (Haguenoer et al., 1975a, b, c). In three human volunteers who inhaled acetonitrile for four hours, only one showed measurable urinary thiocyanate (Pozzani et al., 1959). The delay of onset of symptoms in humans (Amdur, 1959; Pozzani et al., 1959) suggests that acetonitrile is only slowly metabolizd to free cyanide.

Inhalation of 655 ppm of acetonitrile vapor by rats during five seven-hour days of exposure per week for 13 weeks (90 days) produced significant tissue changes in the kidney, liver and lung. One rat had a cerebal hemorrhage. Monkeys who inhaled 2510 or 350 ppm of acetonitrile vapor, on autopsy, showed cerebral hemorrhage and lung congestion. Dogs who inhaled 350 ppm of acetonitrile showed significant weight loss and lung changes (Pozzani et al., 1959). Rats who inhaled 2800 ppm of acetonitrile vapors for 2 hours per day for 5 days displayed difficulty in breathing, impairment of renal function, paralysis of extremities, severe loss of body weight, and hemorrhages in the lung and brain (Haguenoer et al., 1975b).

The wide range of acute toxic effects of acetonitrile and the degenerative tissue changes seen in subacute studies raise a level of concern regarding the possiblity of adverse effects of acetonitrile upon prolonged exposure. The Committee recommends that acetonitrile be tested for possible chronic effects.

Epidemiology

The Committee recommends that epidemiological investigations be carried out on persons involved in the production and use of acetonitrile.

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Anon. 1975. Chemical Marketing Reporter. July 14, p. 3, 17.

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Marine D., Rosen, S. H. And Cipra, A. 1933. Further studies on the erophthalmas in rabbits produced by methyl cyanide. Proc. Soc. Exptl. Biol. Med. 30:649–651.

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Stobaugh, R. B., et. al. 1971. Acrylonitrile: How, where, who-future. Hydrocarbon Processing 40(1):109–120.

Szabo, S. and E. S. Reynolds. 1975. Structure-activity relationships for ulcerogenic and adrenocorticolytic effects of alkyl nitrile, amines, and thiols. Environ. Hlth. Perspec. 11:135–140.

Williams, R. T. 1959. Detoxication metabolism. 2nd Ed. John Wiley and Sons, Inc. New York.

Aniline and Chloro-, Bromo-, and/or Nitro- Anilines

Recommended Studies:
Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Environmental Effects
Epidemiology

Category Identification:

This category includes aniline and aniline substituted in one or more positions with a chloro, bromo, or nitro group, or any combination of one or more of these substituent groups. Excluded from the category are anilines substituted in one or more positions with a group other than a chloro, bromo, and/or nitro group, irresepctive as to whether a chloro, bromo, and/or nitro group also is present. This category includes, but is not limited to, those chemicals listed in Table A. Physical and chemical information is found in Table A.

Reasons for Recommendations:

In general, none of the chemicals in this category has been adequately tested for human health or environmental effects. The results from limited studies, however, raise a level of concern regarding their potential for producing toxic effects. Most category members probably have the ability to induce methemoglobinemia. The parent aniline compound has been reported to be carcinogenic in laboratory animals and other category members have a high suspicion of carcinogenicity. A number of the members have been shown to be mutagenic. Given these demonstrated adverse health effects, the untested and inadequately tested members of the category must be regarded as suspect until each has been appropriately studied. Based on the suspect nature of the category members, on the relatively high production volumes (see Table B) and on the potential for environmental release and human exposure, the following studies are recommended.

Effects of Concern

Carcinogenicity

Aniline has been reported to be carcinogenic in both sexes of treated rats (NCI, 1978b). A tumor similar to that produced by aniline was observed in rats treated with *p*-chloroaniline, although the incidence was not statistically significant (NCI, 1979). 2,4,6-Trichloroaniline has been reported to induce a significant increase in vascular tumors in male mice (Weisburger et al.,

1978). The chemical 4-chloro-2-nitroaniline is regarded with special suspicion since it is a nitro analog of the carcinogen 4-chloro-o-phenylenediamine (NCI, 1978a). The suspect nature of aromatic amines (Clayson and Garner, 1976), in general, and the high level of suspicion of certain specific category members, in particular, raises sufficient concern that the Committee recommends that chemicals within this category be tested for carcinogenicity.

Mutagenicity

A number of category members have been reported to be mutagenic (Prasad and Pramer, 1969; Prasad, 1970; Garner and Nutman, 1977; Romanova and Rapoport, 1971; Kappas, 1978). These findings cast suspicion on the remaining untested or inadequately tested members. The Committee recommends that appropriate tests, which consider both somatic and germinal effects, be undertaken to assess the mutagenic potential of members of this category.

Teratogenicity

No studies were found in the literature on the teratogenic effects of members in this category. Although minimal cyanosis may not produce overt effects in exposed pregnant women, possible adverse consequences on the fetus and embyro are unstudied. Because of the potential of occupational exposure of pregnant women coupled with the known toxicity and systemic absorption of many category members, teratogenic effects should be assessed. The Committee recommends that appropriate tests, which consider both morphological and functional effects, be undertaken to assess the potential teratogenicity of members of this category.

Other Chronic Effects

Aromatic amino and nitro compounds are effective inducers of methemoglobinemia, although the intensity of induction is related to the toxicity of individual compounds, experimental species, and conditions of test. Humans are particularly sensitive to compounds that induce methemoglobinemia. Methemoglobinemia has been reported in humans from exposure to aniline, *m*-nitroaniline, and *p*-nitroaniline (de Bruin, 1976). Systemic absorption may occur by inhalation or through intact skin. The Committee recommends that members of this category be assessed for adverse chronic health effects, with particular emphasis on blood and nervous system disorders.

Environmental Effects

The halogenated anilines, certain nitroanilines and all halogenated nitroanilines appear to have potential for adverse effects on plant and animal life (Schafer, 1972; Corke and Thompson, 1970; Julin and Sanders, 1978; Rashid and Mayandon, 1974; Rusakov, 1968; Thompson and Corke, 1969; Verschueren, 1977). Bioaccumulation varies considerably with members of this category; the octanol-water partition coefficients are intermediate in value (log P ranges up to about 3.0). The occurrences of residues and their persistence in water and soil suggest a continuous and highly dispersive discharge into the environment (Anagnostopoulos et al., 1978; Bollag and Russell, 1976; Corke and Thompson, 1979; Fuchsbichler et al., 1973; Greve and Wegman, 1975; Iliseasn and Stefanescu, 1974; Kaufman et al., 1973; Korte et al., 1978; Meijers and Van der Leer, 1976; Minard et al., 1977; Mueller and Korte, 1974; Smith and Sheets, 1966; Thompson and Corke, 1969; and Verschueren, 1977).

Studies are needed to establish the potential for exposure of each member of this category in water, fish and wildlife, food chain organisms and primary producers. Since conflicting reports of the ability of animals, plants and microbes to metabolize and tolerate these chemicals appear in the literature cited above, further study is recommended by the Committee to clarify the fate, persistence and biotransformation products of these substances in the environment. Where significant exposures exist, the Committee recommends short and long term testing to characterize the nature of toxicity of the bromo-, chloro-, and/or nitro substituted anilines that are released into the environment.

Epidemiology

No information is available on the chronic effects produced in humans exposed to members of this category. The Committee recommends that epidemiologic studies be undertaken to assess the possible adverse, chronic health effects for those category members where there has been or is significant human exposure.

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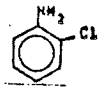
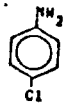
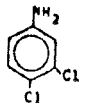
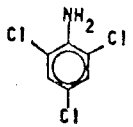
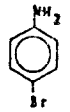
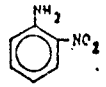
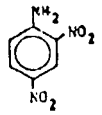
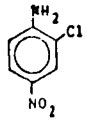
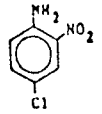
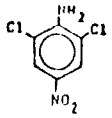
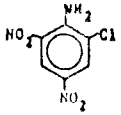
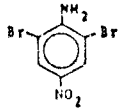
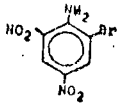
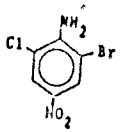
Table A

Aniline and Chloro-, Bromo-, and/or Nitro- Anilines

Selected Properties

Compound	CAS No.	Structure	Molecular Weight	Log Octanol/Water Partition Coefficient[a]	Vapor Pressure[b]
Aniline	142-04-1		93.12	0.90-0.98	1 mm at 34.8°C
o-Chloroaniline	95-51-2		127.57	1.90	1 mm at 46.3°C
m-Chloroaniline	108-42-9		127.57	1.89	1 mm at 63.5°C
p-Chloroaniline	106-47-8		127.57	1.83	1 mm at 59.3°C
3,4-Dichloroaniline	95-76-1		162.03	2.69	?
2,4,6-Trichloroaniline	634-93-5		196.475		1 mm at 124°C

p-Bromoaniline	106-40-1		172.04	2.26	?
o-Nitroaniline	88-74-4		138.12	1.44-1.83	1 mm at 104°C
m-Nitroaniline	99-09-2		138.12	1.37	1 mm at 119.3°C
p-Nitroaniline	100-01-6		138.12	1.39	1 mm at 142.4°C
2,4-Dinitroaniline	97-02-9		183.12	?	?
2-Chloro-4-nitro-aniline	121-87-9		172.57	?	?
4-Chloro-2-nitro-aniline	89-63-4		172.57	?	?

2,6-Dichloro-4-nitroaniline	99-30-9		207.02	?	?
2-Chloro-4,6-dinitroaniline	3531-19-9		217.57	?	?
2,6-Dibromo-4-nitroaniline	827-94-1		295.94	?	?
2-Bromo-4,6-dinitroaniline	1817-73-8		262.03	?	?
2-Bromo-6-chloro-4-nitroaniline	99-29-6		251.48	?	?

Footnotes

a. Leo et al. 1971. Partition coefficients and their uses. Chem. Rev. 71:526-616.

b. Handbook of Chemistry and Physics. 1976. 57th Ed. Weast, R.C., Ed. Chemical Rubber Co., Cleveland, O.

Table B

Aniline and Chloro-, Bromo-, and/or Nitro- Anilines

Chemical-Economic Information

Compound	U.S. Production lbs./yr.	Imports lbs./yr.	Occupational Exposure[a] (Persons)	Major Uses	Comments
Aniline	400 million[b]	Unknown	1,258,600 Rank: 158	Dye intermediate	Exposure to aniline hydrochloride causes methemoglobinemia and cyanosis (Hamblin, 1963; Windholz, 1976). Aniline hydrochloride is carcinogenic to male and female Fischer 344 rats (NCI Tech. Rpt. 78-1385, 1978).
o-Chloroaniline	Unknown	368,861[e]	18,138 Rank: 2263	Dye and agricultural chemical intermediate	Methemoglobin formation was reported in rats (Watanabe, 1976) and cats (McLean, 1969) exposed to *o*-chloroaniline. A moderate increase in the frequency of back mutation in Aspergillus nidulans was reported (Prasad, 1969)
m-Chloroaniline	> 1,000[c]	210,319[e]	Unknown	Dye and agricultural chemical intermediate	Methemoglobin was reported in mice (Nomura, 1975) and rats (Vasilenko, 1972) after exposure to *m*-chloroaniline. An increased rate of back mutations in Aspergillus nidulans was reported (Prasad, 1970).
p-Chloroaniline	> 2,000[c]	104,631[e]	Unknown	Dye and agricultural chemical intermediate	Methemoglobin was reported in cats (McLean, 1969), mice (Nomura, 1975), and rats (Zvezdai, 1972) after exposure to *p*-chloroaniline. An increased rate of back mutations in Aspergillus nidulans was reported (Prasad, 1970). A bioassay produced suggestive evidence for the carcinogenicity of *p*-chloroaniline in rats and mice (NCI Tech. Rpt. 79-1745, 1979).
3,4-Dichloroaniline	Unknown	Unknown	Unknown	Dye and agricultural chemical intermediate	An increased rate of back mutations in Aspergillus nidulans after exposure to 3,4-dichloroaniline was reported (Prasad, 1970).
2,4,6-Trichloroaniline	Unknown	Unknown	Unknown	Dye intermediate	A significant increase in vascular tumors was reported in male mice exposed to 2,4,6-trichloroaniline (Weisburger, 1978).

p-Bromoaniline	Unknown	Unknown	1,744 Rank:5,991	Dye intermediate	Methemoglobin was reported in cats after exposure to *p*-bromoaniline (McLean, 1969).
o-Nitroaniline	> 1,000 (c)	Unknown	400 Rank: 5895	Dye intermediate	Methemoglobin was reported in rats after exposure to *o*-nitroaniline (Watanabe, 1976). The compound was reported to be mutagenic in Salmonella typhimurium TA 1538 (Garner, 1977).
m-Nitroaniline	5,000 (c)	42,046 (e)	Unknown	Dye intermediate	*m*-Nitroaniline was reported to induce methemoglobin in humans and experimental animals (de Bruin,1976). The mutagenicity of the compound was reported in Salmonella typhimurium TA 1538 (Garner, 1977) and Actinomyces sphaeroides (Romanova, 1971).
p-Nitroaniline	8.6 million (c)	2.9 million (c)	800 Rank: 5282	Intermediate for antioxidants, dyes, and gasoline gum inhibitors	Exposure to *p*-nitroaniline was reported to produce methemoglobin formation in rats (Watanabe, 1976) and dogs (Patty, 1963). The compound was reported to be mutagenic in Salmonella typhimurium TA 1538 (Garner, 1977).
2,4-Dinitroaniline	1,000 (d)	300,000 (e)	Unknown	Dye intermediate	2,4-Dinitroaniline was reported to be mutagenic in Salmonella typhimurium TA 1538 (Garner, 1977
2-Chloro-4-nitroaniline	> 2,000 (d)	485,000 (e)	2,739 Rank:4,054	Chemical intermediate	—
4-Chloro-2-nitroaniline	5,000 (d) (d,f) 211,000	90,000 (e) (e,f) 156,000	Unknown	Pigment intermediate	4-Chloro-2-nitroaniline is a nitro analog of the carcinogen 4-chloro-*o*-phenylenediamine (NCI Tech. Rpt. 78-1313, 1978).
2,6-Dichloro-4-nitroaniline	Unknown	Unknown	Unknown	Fungicide and dye intermediate	2,6-Dichloro-4-nitroaniline was reported to induce somatic recombination in Aspergillus nidulans (Kappas, 1978).

2-Chloro-4,6-dinitroaniline	Unknown	24,000 (e)	Unknown	Unknown	—
2,6-Dibromo-4-nitroaniline	> 5,000 (d)	Unknown	Unknown	Unknown	—
2-Bromo-4,6-dinitroaniline	> 150,000 (d)	Unknown	Unknown	Dye intermediate	—
2-Bromo-6-chloro-4-nitroaniline	> 1,000 (d)	Unknown	Unknown	Unknown	—

Footnotes

[a]National Occupational Hazards Survey (NOHS). National Institute for Occupational Safety and Health, Cincinnati, Ohio, 1977.

[b]U.S. International Trade Commission (Reported 1975 Data), 1977.

[c]Toxicology Data Bank (Reported 1975 Data), National Library of Medicine, National Institutes of Health.

[d]U.S. International Trade Commission, Synthetic Organic Chemicals, U.S. Production and Sales (1977), 1978.

[e]U.S. International Trade Commission, Imports of Benzenoid Chemicals and Products.

[f]Reported as Azoic Diazo Component 9 Base.

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*Antimony, Antimony Sulfide, Antimony Trioxide**

Recommended Studies:
Carcinogenicity
Teratogenicity
Mutagenicity
Other Chronic Effects, including reproductive effects
Environmental Effects
Epidemiology

Physical and Chemical Information:
Antimony, CAS No. 7440–36–0, At. Weight: 121.75.
Antimony sulfide, CAS No. 1345–04–6, Molecular Weight: 339.6.
Antimony trioxide, CAS No. 1309–64–4, Molecular Weight: 291.5.

Reasons for Recommendations:

Production, Release, and Exposure: In the U.S. production of antimony in 1976 was over 29 million pounds from ore and approximately 40 million pounds from recycled metal (NIOSH, 1978). For antimony trioxide, U.S. production for 1978 was projected to be 70 million pounds (Hishida, 1977). No data on antimony sulfide were found. The amount of environmental release of antimony, antimony sulfide and antimony trioxide is not known.

NIOSH estimates that 1,350,000 workers are exposed to antimony, 81,793 workers to antimony trioxide, and 1,221,000 to antimony sulfide (NIOSH 1977, 1978). Besides the occupational exposure of antimony and antimony-containing compounds, there are other human exposures. Antimony may be released to the atmosphere from the mining, hauling, and smelting or ore, from the use and disposal of products containing antimony, and from petroleum and petroleum products, coal, and concrete. Ninety percent of the antimony trioxide consumed annually in the United States is used as a flame retardant. A possible measure of exposure is a recent report wherein antimony has been measured in hair of residents of Canada with the following

* Although this rationale supports the designation of antimony, antimony sulfide and antimony trioxide, each of these substances is listed individually on the Section 4(e) Priority List.

results for mean levels in ppm: rural residents, 7.9; urban residents, 9.7; and Canadians residing near lead smelters, 14.6. (Chattopadhyay et al., 1977).

Physical and chemical characteristics suggest that antimony trioxide, when released, will largely accumulate in the soil/sediment system. Monitoring data confirm this prediction with the highest concentrations in solid wastes from processing (Elinder and Friberg, 1977; Schwitzgebel et al., 1978) and in the soil around processing locations (Crecelius et al. 1974). In aquatic sites, concentrations in water are low (A.D. Little Inc., 1976; Shuman et al., 1977) or are associated with particles larger than 0.45 um (Strohal et al., 1975). In polluted sites, sediments can have 10–150 times the concentration as in unpolluted sites (De Goeij et al., 1974; Skei et al., 1972).

Effects of Concern

Carcinogenicity

A large number of animal studies have been reported on various antimony compounds (NIOSH, 1978). Although no carcinogenic effects were demonstrated, the studies are considered to be inadequate by today's testing standards for detecting carcinogenic activity. One study of exposed antimony workers suggests that they may be at increased risk to lung cancer (NIOSH, 1978). No other information was found regarding the potential carcinogenic effects resulting from exposure to antimony compounds. The long-term effects of low-level exposure are of particular concern because of the use of antimony trioxide as a flame retardant in consumer goods, which may lead to widespread human exposure.

Based on the lack of adequate carcinogenicity data on antimony compounds coupled with the opportunity for their wide human exposure, the Committee recomments these substances be tested for carcinogenicity.

Mutagenicity

Antimony trioxide, antimony pentachloride, and antimony trichloride were tested for mutagencity by the rec-assay procedure and found to be positive; that is, they inhibited more strongly cellular growth of a recombinant-deficient strain of *B. subtilis* (M45) than that of a wild one (H17). These results indicate DNA-damaging capacities of these compounds (Kanemutsu and Kada, 1978).

Paton and Allison (1972) report that some compounds of antimony cause chromosome aberrations in plants, insects and cultured human cells. Coupled with the possible reproductive effects in humans reported by Belyayeva and discussed below, these data suggest that antimony compounds may be mutagenic. The Committee, therefore, recommends that antimony, antimony sulfide and antimony trioxide be tested for mutagenicity, including both germinal and somatic effects.

Teratogenicity

Only limited animal data are available on the possible teratogenicity of antimony, antimony trioxide and antimony sulfide. Bradley and Frederick (1941) noted frequent abortions in rabbits given repeated high oral doses of metallic antimony. Belyayeva (1967) reported that rats repeatedly exposed to 250 mg/cubic meter of antimony trioxide by inhalation produced fewer offspring than controls. No changes were observed in the maternal reproductive system. However, Casals (1972) reported that no antimony was detected in rat fetuses whose mothers had received antimony dextran glycoside intramuscularly during gestation. James et al. (1966) reported on four yearling ewes fed antimony potassium tartrate at 2 mg/kg of body weight for 45 days or throughout gestation. All ewes fed the antimony gave birth to normal, full term lambs. Upon autopsy, no adverse effects were observed in the ewes.

Suggestive evidence of possible adverse effects in humans was reported by Belyayeva (1967) who observed an excess incidence of spontaneous abortions, premature births and gynecologic problems in female workers exposed to dusts of antimony metal, antimony trioxide and antimony pentasulfide.

Based on the lack of adquate data and possible widespread human exposure, the Committee recommends teratogenicity testing on antimony, antimony trioxide, and antimony sulfide.

Other Chronic Effects

Pneumoconiosis and skin irritation have been reported in humans exposed chronically to antimony trioxide (NIOSH, 1978). Although two reports (NIOSH, 1978; Elinder and Friberg, 1977) summarize a number of adverse effects (e.g., shortened life span and respiratory disorders in rats, degeneration of the myocardium in rats and rabbits, and degeneration of the kidney and liver in rabbits) in experimental animals exposed to various antimony compounds, there have been no adequate long-term studies to assess the chronic health effects resulting from exposure to antimony compounds.

Given the suggestion of reproductive effects, the general lack of data on other health effects and the potential for wide human exposure, the Committee recommends that antimony and the antimony compounds be tested for their chronic health effects, including reproductive effects.

Environmental Effects

High levels of antimony trioxide observed in soil suggest the possibility of risk to terrestrial plants, to other food chain organisms and to soil microorganisms. The basis for this possibility is the presence in soil of antimony at concentrations higher than levels known to cause toxicity to aquatic organisms. There is insufficient antimony toxicity data on terrestrial plants and soil microorganisms. If terrestrial plants bioconcentrate antimony, testing of other organisms in terrestrial food chains would be appropriate. If testing on soil microorganisms shows a risk of interference with nutrient cycling, then further study may be needed.

Considerable data exist which indicate that acute toxicity to aquatic organisms occurs at concentrations which are generally higher than expected environmental levels (A.D. Little, Inc., 1976; Hildebrand et al., 1976). However, acute toxicity is commonly within two orders to magnitude of levels expected in the environment, and chronic toxic effects can occur at 100–1000 times lower concentrations of some chemicals than acute toxic effects (Biesinger and Christensen, 1972: Brungs et al., 1977; Claus, 1976; Benoit, 1976). In addition, antimony is persistent and may bioaccumulate (A.D. Little, Inc., 1976).

Since antimony and antimony compounds are likely to be released to the environment during production and use, and because of their persistence, the Committee recommends that these chemicals be tested for possible environmental effects. The use of antimony trioxide as a flame retardant in many applications may lead to environmental release upon use and disposal of the flame retarded materials.

Epidemiology

Occuptional studies have been conducted predominantly on the acute toxic effects of antimony, antimony trioxide and antimony sulfide. There is little information on chronic effects in humans from exposure to low levels of antimony, antimomy trioxide, and antimony sulfide over an extended

period of time. Because of its long-term use, high human exposure, and demonstrated effects in animals, epidemiological studies may be particularly important in assessing the human health effects of antimony, antimony trioxide and antimony sulfide.

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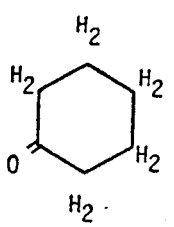
Cyclohexanone

Recommended Studies:
- Carcinogenicity
- Mutagenicity
- Teratogenicity, including behavioral studies in the offspring
- Other Chronic Effects, including reproduction and neurological studies
- Environmental Effects
- Epidemiology

Physical and Chemical Identification

CAS Number: 108–94–1

Structural Formula



Vapor Pressure: 10 mm at 38.7°C.
Log Octanol/Water Partition Coefficient: 0.81 (Leo et al., 1971)
Empirical Formula: $C_6H_{10}O$
Molecular Weight: 98.15
Boiling Point: 155.65°C

Soluble in water, alcohol, ether, acetone, benzene and chloroform.

Reasons for Recommendations:

Production, Release and Exposure

Cyclohexanone is produced in very large quantities with 783 million pounds in 1972 (ITC, 1974); 651 million pounds in 1974 (ITC, 1976); 554 million pounds in 1975 (NIOSH, 1978) and 641 million pounds in 1976 (ITC, 1977). Because of its widespread use as an industrial solvent, as well as a multiplicity of other uses, cyclohexanone has a high occupational exposure.

NIOSH estimates that 1,190,000 workers are potentially occupationally exposed (NIOSH, 1977). The estimated annual environmental release of cyclohexanone is 51 million pounds (Lande et al., 1976). General population exposure is potentially high since cyclohexanone is used as a solvent in numerous consumer products (e.g. stain, spot and paint removers; lacquer thinner; polishes; adhesives). It is also used in resins and lubricating oils.

Effects of Concern

Carcinogenicity

No carcinogenicity studies of cyclohexanone were found. Due to the potentially large human exposure and the indication of biological activity, as seen in the teratogenic and cytogenic activity discussed below, the Committee recommends carcinogenicity testing.

Mutagenicity

Possible cytogenic activity of cyclohexanone was demonstrated by means of human leukocyte cultures, according to the work of Collin (1971). Further studies are needed to assess mutagenicity including possible germinal and somatic effects. The Committee recommends mutagenicity testing.

Teratogenicity

Fertilized chicken eggs were utilized by Griggs et al. (1971) to study exposure to cyclohexanone vapor at an undescribed concentration. Three groups of eggs were incubated for 96 hours along with appropriate controls. The experimental groups were then exposed to cyclohexanone vapors for 3, 6, and 12 hours respectively (Study A). Two other groups were exposed for 3

and 6 hours prior to incubation (Study B). Both of the latter groups and the 6-hour exposed embryos of the former weighed significantly less than their controls. Chemical studies of the 12-hour exposed embryos revealed decreased serum calcium and elevated inorganic phosphate and SGOT; which suggested to the authors a condition of tetany and perhaps liver dysfunction. Four groups, two from each of Studies A and B, were permitted to hatch at 21 days incubation. The mortality of the experimental subjects ranged from 20% to 50% while the control chick mortality was only 10% to 20%. Survivors of the 3-hour exposed chicks of Study A could not maintain posture; could not walk; and, when disturbed, attempted to escape with a violent, somewhat spastic, sliding motion. All chicks were normally alert and normal in appearance, except for inward-curled toes. The authors stated that "no animals had gross abnormal anatomical difficulties, such as would be expected with other chemical teratogens." They concluded that these chicks suffered from what may well be an upper motor neuron lesion which produced marked neurological damage or covert embryopathy. The authors summarized by stating that cyclohexanone is functionally, rather than morphologically, teratogenic in the developing chick.

Weller and Griggs (1973), in a separate study, exposed two groups of embryonated eggs at 0 and 96 hours incubation age for 3, 6, and 12 hours to cyclohexanone vapors, and the controls to normal air. The results were the same as the previous study, except that the experimental group chicks that hatched were normal at first, and then developed severe locomotor difficulties within a few hours. In the paper they stated that the functional, rather than gross, teratogenic effect in the chick embryo may be clinically significant for man. Because of the extremely high production and release of this compound, and the significant occupational and general human exposure, teratogenicity studies including behavioral studies in the offspring are recommended by the Committee.

Other Chronic Effects

Cyclohexanone has been shown to produce irreversible changes in animal studies by Rengstorff et al. (1972). During a guinea pig skin sensitization study with acetone and cyclohexanone, the formation of cataracts by both agents in subcutaneous and cutaneous routes was an unexpected finding. This finding was confirmed in a subsequent study with cataracts appearing at three months when cyclohexanone was administered subcutaneously, and six months with cutaneous application. Both the controls and an additional 500 guinea pigs from the same animal colony receiving similar animal care were negative.

In addition to the neurological indications of the studies in chicks by Weller and Griggs (1973) and Griggs (1971) described above, neurological effects are suggested by other studies, summarized by Treon et al. (1943). Effects observed include rhythmic clonic convulsions, paralysis, and death in rabbits and excitation, tremors, *paresis* of the hind quarters, marked hypothermia and muscular convulsions, which did not cease until death, in mice. Also erythema, nerve irritation, wheal formation, and hyperemia following application of cyclohexanone upon human skin.

Dobrinskiy (1971) studied inhalation of low levels of cyclohexanone vapor in human subjects and found a threshold reflex of electrical activity at 0.06 mg/m^3 1n EEG measurements.

Adequate long term studies on cyclohexanone are needed. The Committee recommends chronic effects testing with particular emphasis on neurological and reproductive effects.

Epidemiology

Due to the irreversible changes reported in animal studies and the high production and human exposure estimates cited above the Committee recommends that epidemiological studies be conducted.

Environmental Effects

Although cyclohexanone has been detected in both air and water, environmental effects information is incomplete, at best.

Crisp et al. (1967) found that cyclohexanone produced narcosis in the barnacle larvae *Elininius modestus* at water saturation levels within 15 minutes.

Saslavasky and Ishay (1973) reported 25 to 50 percent mortality among the oriental hornet *Vespa orientalis* in both 2–12 day old and 12–30 day old colonies exposed to cyclohexanone (although the precise route of exposure could not be ascertained from the publication).

Verschueren (1977) reported that cyclohexanone began to inhibit cell multiplication in *Microcystis aeruginosa* at 52 mg/liter; and that cyclohexanone begins to inhibit cell multiplication in *Pseudomonas putida* at 180 mg/liter of water.

While the potential for bioaccumulation may be low (Neely et al., 1974; Leo et al., 1971), actual experimental data on rate of uptake and depuration could not be found. Since the quantity estimated to be released to the environment is relatively high and represents a continuous exposure to both terrestrial and aquatic life, the Committee recommends environmental effects testing.

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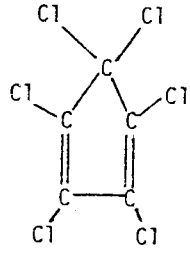
Hexachloroeyclopentadiene

RECOMMENDED STUDIES
Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Evironmental Effects
Substance Identification: CAS No. 77–47–4

Structural Formula



Molecular formula C_6Cl_6
Molecular weight: 272.8
Boiling point: 239°C
Melting point: 9.6°C

Hexachlorocyclopentadiene (hex) is a pale yellow nonflammable liquid with very pungent odor. It solubility in water is 2.10 ppm at 25°C and 2.25 ppm at 35°C. Hex is a highly reactive compound that undergoes substitution and addition reactions to give many products.

Reasons for Recommendations

Production, Release, and Exposure

Hexachlorocyclopentadiene is a highly reactive, highly chlorinated, important intermediate with no uses of its own (Ungrade and McBee, 1958). The current major uses of hex are as an intermediate in the manufacture of cyclodiene pesticides, primarily endosulfan and Pentac(R); and flame retardants for resins and plastics. Numerous other uses are listed in the patent literature but seem to be of technological interest only. Before restrictions were placed on some of the major cyclodiene insecticides (chlordane, aldrin, dieldrin, heptachlor, isodrin, endrin, mirex and kepone) an estimate was made that over 50 million pounds per year of hex were used as an intermediate (Whetsone, 1964). Current production for this use must be much lower since only endosulfan and Pentac(R) are in use. On the other hand, the manufacture of flame-retardant polyester resin formulations seems to be increasing at the rate of 10 percent annually. An estimated 8.3 million pounds of hex was used to produce chlorendic acid and anhydride in 1974 for flame retardants. (EPA, 1978).

The most likely route of entry into the environment is from the manufacturing process of hex or products made from hex. It has been detected in factory air and plant effluents, (Spehar, et al. 1977; EPA 8EHQ–0378–109)) In addition, the disposal of large quantities of hex presents a serious problem. Recently, sewage treatment plant workers were exposed to high doses of hex resulting from clandestine diposal of this compound (NIOSH, 1978).

Effects of Concern

Carcinogenicity

No carcinogenicity test data were found in the searched literature. The Committee, therefore, recomends that hex be tested in view of its high exposure potential and suspect chemical structure. Chemically related compounds—dieldrin, heptachlor and chlordane—were found to induce liver tumors in mice following oral administration (NCI, 1977a; NCI, 1977b; NCI, 1977c).

Mutagenicity

Although hex was reported to be non-mutagenic in *Escherichia coli* K12 in the presence of a mammalian metabolic activation system containing mouse liver microsomes (Bonse et al., 1977), additional testing employing other systems is required to evaluate the mutagenic potential of this chemical.

Teratogenicity

No teratogenicity test data are found in the searched literature. The Committee, therefore, recommends that the appropriate teratogenicity studies be undertaken.

Other Chronic Effects

The acute toxicity of hex in mammals and man is relatively well documented (Treon et al, 1955; EPA, 1978; NIOSH, 1978; EPA 8EHQ–0278–0064). It is concluded from the results of several studies that hex is a highly toxic material by inhalation (Treon et al., 1955). No adequate chronic toxicity studies have been identified in the searched literature. Treon et al. (1955) observed degenerative changes in the brain, heart, liver, kidney and adrenal glands in the various species tested but the number of animals and duration of

experiments were inadequate for evaluation.

Environmental Effects

Information on the behavior of hex in aquatic and terrestrial ecosystems is inadequate for an assessment of hex's environmental impact (NRC, 1978). Hex seems to persist in sludge, ground water and aquatic environments associated with its use and disposal (NIOSH, 1978; EPA, 1978; EPA 8EHQ-0178-0037; EPA 8EHQ-0578-0147). Bioaccumulation in fish and other organisms has been reported (Spehar et al., 1977; Lu et al., 1975; EPA 8EHQ-1177-0013; EPA 8EHQ-0378-0054; EPA 8EHQ-0278-0061; EPA 8EHQ-0378-0099). The potential for biological uptake and ecological magnification of this compound suggest the need for further testing to determine the biological significance of exposure to fish, wildlife and food chain organisms (EPA, 1978). Acute effects on fish, wildlife and food chain organisms are insufficient indicators of the nature of toxicity of hexachlorocyclopentadiene. Since it appears to be persistent and to bioaccumulate, particular emphasis of testing should be placed upon long-term chronic effects.

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Also, from the Environmental Protection Agency's Public Reading Room, the following TSCA Section 8(e) Notices of substantial risk of injury to health or the environment: 8EHQ-0178-038, 8EHQ-0378-0110, 8EHQ-0678-0208, 8EHQ-0678-0189P.

Isophorone

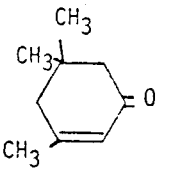
Recommended Studies

Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Epidemiology

Physical and Chemical Identification

CAS number: 78-59-1

Structural formula



Molecular formula: $C_9H_{14}O$
Molecular weight: 138.2
Melting point: −8.1° C
Boiling point: 215.2° C
Vapor pressure: 0.31mm Hg @ 20° C

Isophorone (3,5,5-trimethylcyclohex-2-ene-1-one) is an unsaturated cyclic ketone. It is a clear liquid with a peppermint-like odor and a cooling taste. It is very slightly soluble in water.

Reasons for Recommendations

Production, Release, and Exposure

Isophorone is used as a solvent for vinyl resins, lacquers, and finishes; as a chemical intermediate in dyes, plasticizers, inhibitors, rubber chemicals, and flotation agents and as a pesticide (Hawley, 1971; NIOSH 1978a). Although production figures are not available estimated worker exposure is over 1.5 million (NIOSH, 1977). Isophorone has been identified in several water supplies, including one drinking water supply at 1.5–2.9 ug/liter (Shackelford and Keith, 1976; EPA, 1975).

Effects of Concern

Carcinogenicity

As an *alpha, beta-* unsaturated ketone isophorone is expected to have a strong tendency to undergo nucleophilic addition to its carbon-carbon double bond, i.e., it may behave as a direct alkylating agent. This expected reactivity may be lessened somewhat by steric hindrance by the methyl group on the double bond but only actual biological testing can determine the net effect ot these opposing tendencies.

Because of its possible alkylating potential, its high exposure and the lack of carcinogenicity test data, the Committee recommends that isophorone

be tested to determine its carcinogenic potential.

Mutagenicity

No mutagenicity test data was found in the searched literature. The possible alkylating activity of isophorone, mentioned above, suggests that this chemical may have mutagenic potential. The Committee, therefore, recommends mutagenicity testing.

Teratogenicity

No information is available on the teratogenicity of isophorone. Therefore, testing is recommended.

Other Chronic Effects

Information available on the toxicity of isophorone is limited to an acute study and a six week study on rats and guinea pigs. (Smyth and Seaton, 1940; Smyth et al., 1942). Irritation of eyes, nose, and throat in human subjects was noted by Silverman et al. (1946) and workers exposed at 5–8 ppm complained of fatigue and malaise (NIOSH, 1978).

Owing to the high exposure potential of this chemical and the lack of information on its toxicity, the Committee recommends testing for other chronic effects.

Epidemiology

There is no information on chronic effects in humans from exposure to low levels of isophorone. Because of the high occupational exposure, epidemiological studies may be particularly important in assessing the human health effects of isophorone.

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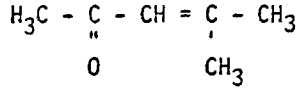
Mesityl Oxide

Recommended Studies:
- Carcinogenicity
- Mutagenicity
- Teratogenicity
- Other Chronic Effects
- Epidemiology

Physical and Chemical Information

CAS No.: 191–79–7

Structural Formula



Boiling point: 129.76° C
Vapor pressure: 10 mm at 26° C
Log octanol water partition coeff.: 1.24
Molecular formula: $C_6H_{10}O$
Molecular weight: 98.15

This unsaturated acyclic ketone is an oily liquid at room temperature. It has a characteristic peppermint odor (Rowe and Wolf, 1963). It is soluble in water, acetone, alcohol and ether.

Reasons for Recommendation

Production, Release, and Exposure

Mesityl oxide is produced commercially by dehydration of diacetone alcohol or by autooxidation of acetone. Annual production figures for the years 1974 and 1975 are 26.8 and 45.7 million pounds, respectively, according to the International Trade Commission (ITC, 1974; ITC, 1975). The chemical is released to the atmosphere during both manufacture and use, mostly from the formulation of surface coatings. These coatings include nitrocellulose, vinyl chloride-vinyl acetate copolymers, synthetic rubber, gums, resins, and ink pastes. It is also used in paint and varnish removers, carburetor cleaners, stain removers, and flotation agents. It is used as an intermediate in the production of lubrication oil additives, plasticizers, and methyl isobutyl ketone. This compound has been detected in automobile exhaust (Rose, 1969; Bellar and Sigsby, 1970; Seizinger and Dimitriades 1972) with maximum levels of 1.5 ppm. Worker exposure to this compound is estimated at 6160 (NIOSH, 1979).

Effects of Concern

Carcinogenicity

Although no studies could be found on the potential carcinogenicity of mesityl oxide, there is evidence to suggest that this compound may have carcinogenic activity.

Mesityl oxide, an *alpha, beta*-unsaturated ketone, is expected to have a strong tendency to undergo nucleophilic addition to its carbon-carbon double bond, i.e., it may behave as a direct alkylating agent. This possible activity as an alkylating agent may be somewhat reduced because of steric hinderance by the methyl groups on the beta carbon; but conclusions about this possible steric effect cannot be made without biological testing. The Committee recommends that mesityl oxide be tested for carcinogenicity.

Mutagenicity

No information could be found in the sources searched. Due to the potential as an alkylating agent, studies to screen

for mutagenic activity are recommended.

Teratogenicity

No information could be found in the sources searched. Studies to test for teratogenicity are recommended.

Other Chronic Effects

Silverman et al. (1946) reported on the human sensory thresholds for mesityl oxide. Twele men and women were exposed to the compound for 15 minutes and irritating concentrations were established at 25, 50 and 50 ppm for eyes, nose, and throat respectively.

Considerable irritation resulted from the dermal exposure of humans to this chemical. This was reported by Specht et al. (1940), as reported in NIOSH (1978)), after laboratory workers working with mesityl oxide complained of irritation of the hands in spite of protective latex gloves.

In acute inhalation tests with mice Hart et al. (1939), as reported in NIOSH (1978), found necrotic spots in liver, lung hemorrhage, alimentary tract distention and death. Smyth et al. (1942) in subchronic tests with guinea pigs and rats reported congested livers and lungs, dialated Bowman's capsules in the kidney, and swollen and convoluted tubular epithelium.

Significant deleterious effects on the rabbit cornea were found by Carpenter and Smyth (1946). Application of 0.02 ml of pure mesityl oxide caused necrosis covering 75 percent of the cornea 18–24 hours later.

Ito (1969) noted leukocytosis in rats and leukopenia and anemia in rabbits exposed to this chemical. The results in rabbits seem to be corroborated by a medical survey of workers which noted the "possibility of anemia and leukopenia" (Ito 1969). No other information could be found in the sources searched. These hematological abnormalities may be early indicators of the effects of mesityl oxide on the hematopoietic system.

Although the effects of mesityl oxide at acute and subchronic levels are well documented there are no reports on the effects of prolonged exposure to this chemical. It is therefore recommended that chronic studies be initiated to evaluate the effects of prolonged exposure with special emphasis on possible blood disorders.

Epidemiology

Because of its human exposure and demonstrated effects on animals, epidemiological studies to assess the human health effects of mesityl oxide should be conducted.

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Smyth, H.F., Jr., J. Seaton, and L. Fischer. 1942. Response of guinea pigs and rats to repeated inhalation of vapors of mesityl oxide and isophorone. J. Ind. Hyg. Toxicol. 24:46–50.

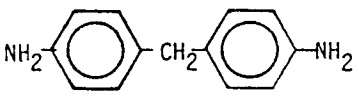
4,4'-Methylenedianiline

Recommended Studies
- Carcinogenicity
- Mutagenicity
- Teratogenicity
- Other Chronic Effects
- Environmental Effects
- Epidemiology

Physical and Chemical Identification

CAS number: 101–77–9

Structural Formula



Molecular formula: $C_{13}H_{14}N_2$, Molecular weight 198.26.

Melting point: 92–93°C, Vapor pressure: Negligible at 25°C.

This pale yellow to cream colored crystalline solid is slightly soluble in cold water and is very soluble in alcohol, benzene and ether. (IARC, 1974).

Reasons for Recommendations

Production, Release and Exposure

Annual US production of 4,4'-methylenedianiline (MDA) is approximately 200 million pounds. Ninety-nine per cent of production is not isolated but is used as an intermediate in the manufacture of isocyanates and polyisocyanates. These are then used in the manufacture of rigid polyurethane foams. The polyisocyanates are also used in the manufacture of semiflexible polyurethane foams. 4,4'-Methylenedianiline is also used as an epoxy resin hardening agent; as a corrosion inhibitor; in the rubber industry as a curative for neoprene and as an antioxidant in footwear; and as a raw material in the production of Qiana nylon, polyurethane elastomers, poly(amide-imide) resins, and azo dyes. (NIOSH, 1976; IARC, 1974; Emmett, 1976). Exposure to the compound in the workplace is estimated to be 5000 persons (NIOSH, 1976) and it is possible that the compound is present in the effluents from manufacture of polyurethane polymers (IARC, 1974).

Effects of Concern

Carcinogenicity

Munn (1967) reported miscellaneous tumors in rats upon intragastric intubation for 5 days per week for 121 days. Schoental (1968 a,b) reported MDA to be a "potential carcinogen" in rats after several intragastric doses. Although highly suggestive of carcinogenicity, these studies are insufficient to establish carcinogenic potential according to present day testing standards.

Steinhoff and Grundmann (1970a) reported a total of 29 benign and 33 malignant tumors in rats given subcutaneous doses of 30–50 mg MDA/kg body weight at one to three week intervals over a period of 700 days. Controls showed 15 benign and 16 malignant tumors. Four hepatomas were reported in treated rats but the exact incidence of tumor types observed was not recorded.

Chemicals very closely related to MDA have been tested in laboratory animals for carcinogenicity and found to be carcinogens.

4,4'-Methylenebis(2-methylaniline) produced a high incidence of benign and malignant liver tumors on repeated gastric intubation into rats (Munn, 1967).

The tumors were not seen in control groups. Similar results were obtained by other investigators feeding the compound to male and female rats (Stula et al., 1971; Stula et al., 1975).

4,4'-Methylenebis(2-chloroaniline) was administered to male and female rats in the diet and produced a high incidence of benign and malignant lung tumors as well as liver tumors (Grundmann and Steinhoff 1970a; Stula et al., 1971; Russfield, 1975; Stula et al., 1975). On subcutaneous (s.c.) injection of the compound in saline into rats, liver and lung cancers were observed in the exposed animals, in contrast to the controls which showed no malignancies (Steinhoff and Grundmann, 1971).

3,3'-Dichloro-4,4'-diaminodiphenyl ether on s.c. injection into rats produced ear duct carcinomas (Steinhoff and Grundmann, 1970b). The parent compound, 4,4'-diamino-dipenylether, on s.c. injection into rats produced 20% incidence of malignant and 24% incidence of benign liver tumors, while in the control group no liver tumors were observed (Steinhoff, 1977).

This does not imply that 4,4'-methylenedianiline must therefore also be carcinogenic, but that additional studies be undertaken. Therefore, the Committee recommends carcinogenicity testing on 4,4'-methylenedianiline.

Mutagenicity

Positive results were reported in a study by Shimizu and Takemura (1976). This report showed that MDA was mutagenic to 2 strains of *Salmonella typhimurium.*

Because of the lack of data and the results of the *Salmonella* experiment, testing for mutagenicity with emphasis on mammalian systems is recommended.

Teratogenicity

In a study by McLaughlin and coworkers the compound was introduced into the yolk sac of the chicken egg at a total dose of 5 mg. Only 30% of the treated eggs hatched compared to 95% in the controls. Most of the chicks that hatched from the treated eggs had abnormalities in their mandibles and leg deformities (McLaughlin et al. 1963). These data suggest teratogenicity and embryotocicity, but this chemical should be tested in mammals where results would be more extrapolatable to humans.

Other Chronic Effects

The most clearly identified human toxicity of 4,4'-methylenedianiline was first observed in people accidentally exposed to the chemical in bread made from contaminated flour (Kopelman et al., 1966 a, b). They suffered rapidly developing hepatitis (termed "Epping jaundice") which cleared up in due course. No residual toxicity was reported for these people following this acute exposure for as long as they were followed. Samples of the contaminated bread fed to a few young mice for a few days produced hepatic necrosis and biliary duct hyperplasia (Kopelman, 1966a).

Toxic hepatitis was reported by McGill and Motto (1974) in men exposed to MDA used as an epoxy resin hardener. Twelve young male workers developed symptoms similar to those of the "Epping jaundice" between 1966 and 1972. Exposure was of short duration (two to three weeks) via inhalation or dermal contact. Inhalation concentrations ranged from 0.1 to 0.0051 ppm. Dermal contact occurred during accidental dispersal of powdered MDA at higher concentrations. Hepatitis was also reported by Williams et al. (1974) in another group of workers using epoxy resins. In this incident six of 300 men were affected. Routes of exposure were suspected to be skin absorption, ingestion and/or inhalation and symptoms appeared from two days to two weeks after exposure. MDA together with 2-nitropropane were considered the causative agents.

Feeding studies in rodents produced liver damage which can be considered parallel to the findings in man (Pludro, 1969, Gohlke and Schmidt 1974; Fukushima et al., 1977; Shinohara et al., 1977). Jaundice was observed within five days in dogs given 5 or 20 Mg/kg total dose of the compound (Rowe, 1974 as cited in McGill and Motto, 1974). In a long-term feeding study in dogs, liver damage was suggested by increased alkaline phosphatase levels and, on autopsy after 5–7 years, cholestasis, inflammation, focal necrosis, and cirrhosis were reported (Deichmann, 1974).

In one study in rats, the suggestion was made that 4,4'-methylene dianiline could cause necrosis of proximal convoluted tubules in the rat (Calder et al., 1973). In cats blindness due to MDA was reported (Schoental 1968b).

In humans, the observation was also made that the chemical can cause contact dermatitis (Emmett 1976) and parallels studies in guinea pigs which also produced skin sensitization when the chemical was given alone or with Freund's complete adjuvant (Pers. comm., Pacific Anchor Chemical Corporation, 1977).

Because of these findings the Committee recommends studies on the chronic toxicity to the liver, kidney, and eye.

Environmental Effects

Evaluation of the effects of this compound on the environment is difficult. Few data on the biodegradation or metabolism of this compound are available. The lack of important physico-chemical data also makes it difficult to predict the behavior of this chemical in biological systems or the environment.

Toxic effects on organisms including bacteria, algae, protozoa, and arthropods vary in their degree of intensity. Toxic concentrations range from 0.25 mg/1 with the arthropod *Daphnia* to 124 mg/1 with the protozoan *Colpoda* (Verschueren, 1977).

Because some of these groups serve as primary producers and act as consumers at low trophic levels in natural food webs it is important to know the bioaccumulation and biomagnification potential and effects, if any, of the chemical. No data on the effects of this compound on other ecologically significant groups could be found in the literature searched. Because of the known high toxicity of this substance and lack of information on its behavior in the environment, the Committee recommends environmental effects testing.

Epidemiology

There is no information available on chronic effects in humans exposed to MDA over an extended period of time. Because of the potentially widespread exposure, epidemiological studies may be particularly important in assessing the human health effects of this compound and are therefore recommended.

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Methyl Ethyl Ketone

Recommended Studies

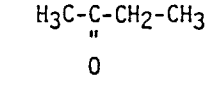
Epidemiology

Chronic Effects, with particular attention to neurological effects

Physical and Chemical Information

CAS No. 78–93–3

Structural Formula



Empirical Formula: C_4H_8O
Molecular Weight: 72.12
Boiling Point: 79.6°C
Melting Point: 86.35°C
Vapor Pressure: 100 mm at 25°C
Log Octanol/Water Partition Coefficient: 0.29

Reasons for Recommendations

Production, Release and Exposure

About 505 million lbs. of methyl ethyl ketone (MEK) are produced annually (Lande et al., 1976). MEK is used primarily as a solvent and is consumed principally by industry. It uses are as a solvent in the industrial coatings industry, in rare metal refining, lube oil dewaxing, printing inks, degreasing and adhesives. NIOSH estimates that about 3 million workers are exposed (NIOSH, 1977).

Ketones occur naturally from biological degradation of organic wastes by soil and water microorganisms. MEK had been identified as a product of the activated sludge treatment of sewage (Malaney and Gerhold, 1962; Abrams et al., 1975) and as a component of the leachate from solid waste (Abrams et al., 1975; Burrows and Rowe, 1975). MEK is also formed as a product of ozonation of 2-methyl-l-butene (Altshuller and Bufalini, 1965). MEK may enter the environment by evaporation from industrial surface coating solutions (Lande et al., 1976). The solvent may be released directly to the atomosphere, incinerated or removed with activated charcoal. MEK emission to the atmosphere can occur from accidental spillage during transport and storage from vapor losses during transfer operations and venting losses from tanks.

MEK, as a short chain methyl n-alkyl ketone, is readily susceptible to microbial degradation. Oxidative degradation studies in pure bacterial cultures of n-alkyl ketones show that the rate of degradation of MEK is second only to that of acetone (Lukins and Foster, 1963; Perry, 1968). MEK has been shown to undergo extensive degradation in mixed cultures and activated sludge systems as well (Lande et al., 1976). Because of its susceptibility to microbial attack, it appears unlikely that MEK will accumulate in aquatic or soil environments. Since its vapor pressure is high, much of this solvent will evaporate into the atmosphere from soils. It is likely to be photochemically degraded to a significant extent. Because of low atmospheric concentration, MEK is not likely to pose significant inhalation hazard to terrestrial animals. Due to its moderate water solubility and its log partition coefficient of 0.26 (Leo et al., 1971), MEK is unlikely to bioaccumulate in food chain organisms. If released into sewage treatment plants, it will be substantially biodegraded. The information available on environmental release, persistence and bioaccumulation factors indicates that MEK does not have a high potential for ecological hazard.

Toxicology

MEK is a normal constituent of human urine (Zlatkis et al., 1973). After acute exposure, elimination of unchanged MEK in expired air may also be a major route of elimination (Schwarz, 1898; Williams, 1959). MEK can be absorbed through the skin or lungs. MEK is irritating to the eyes and nose. It can produce headache, nausea with vomiting and dizziness. It acts as a narcotic or central nervous system depressant. It can cause dermatitis and numbness of fingers and arms (Smith and Mayers, 1944). Its highest tolerable level has been found to be 200 ppm for an 8 hour day (Nelson et al., 1943). It is quite well characterized as to acute

toxicity in laboratory rodents by various routes of administration (Lande et al., 1976). Pathological examination after each exposure of 100,000 ppm revealed corneal opacity and congestion of the lungs, liver, kidneys and brain (Patty et al., 1935). These effects were absent in animals that survived narcosis and were sacrificed 8 days later. Subacute or chronic toxicity studies have not been performed for MEK.

MEK was used as one of several solvents in mutagenicity screenings of pesticides (Shirasu et al., 1976). The pure solvent showed no mutagenic activity.

Pregnant rats were exposed to high concentration of MEK (1000 to 3000 ppm) for 7 hours a day on the sixth through fifteenth days of gestation. Some degree of skeletal abnormalities was found in the fetuses. A low incidence of true terata (Schwetz et al., 1974) was found in the high dose group only.

MEK was applied with benzyl disulfide twice weekly for one year to the skin of mice (Horton et al., 1965). No tumors were found.

Effects of Concern

Chronic Effects

Acute toxicity of MEK is well characterized. However, long term toxic effects of MEK have not been well studied. In light of its acute neurological effects and potential for widespread human exposure, the Committee recommends that chronic studies be performed to assess the effects of long term exposure.

Epidemiology

The long term toxic effects of MEK have not been assessed nor have epidemiologic studies been performed to determine chronic effects of MEK exposure in humans. Because of its acute neurological effects and its extremely high level of exposure, the Committee recommends epidemiological study.

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Methyl Isobutly Ketone

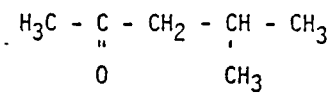
Recommended Studies

Mutagenicity
Teratogenicity
Chronic Effects
Epidemiology

Physical and Chemical Information

CAS No.: 108–10–1

Structural Formula



Molecular Formula: $C_6H_{12}O$
Log Partition Coefficient: 20.6
Molecular Weight: 100.16
Melting Point: −84.7° C
Boiling Point: 116.85° C
Vapor Pressure: 15 mm Hg at 20° C
Water Solubility: 2.04% by weight at 28° C

Reasons for Recommendations

Production, Release and Exposure

Methyl isobutyl ketone (MIBK) is produced commercially by acetone condensation followed by catalytic hydrogenation. The commercial product is 95% pure; principal contaminants are acids, water, alcohols and suspended matter. MIBK production was about 155 million lbs. in 1976 (Lande et al., 1976). It is used principally in industrial coating solvents, in lube oil dewaxing and in rare metal refining. Significant environmental release of MIBK may originate from evaporation of solvent during drying of industrial coatings if adequate incineration and/or emission controls are not employed. NIOSH estimates that 1,853,000 workers are potentially exposed to MIBK (NIOSH, 1977).

MIBK is subject to aerobic biodegradation in the presence of mixed cultures of microorganisms (Lande et al., 1976). However, branching makes it less susceptible to biodegradation than straight chain aliphatic ketones. Its high vapor pressure suggests a strong tendency to enter the atmosphere, where biodegradation does not occur. If discharged as a liquid into sewage treatment plants where biological activity is high, a substantial amount will probably be biodegraded. MIBK does not hydrolyze, but as a branched chain ketone, may be photochemically active. If released directly into water,

MIBK will evaporate with a half-life of 33 hours (MacKay and Wolkoff, 1973). Because of its high vapor pressure and chemical and biological degradation in the environment. MIBK does not appear to pose a hazard to terrestrial animals.

Metabolism

MIBK undergoes oxidative-reductive metabolic conversion (Lande et al, 1976; DiVincenzo et al., 1976). Primary metabolites in guinea pigs are 4-hydroxy-4-methyl-2-pentanone and 4-methyl-2-pentanol (DiVincenzo et al., 1976). Enzymatic ketonic reduction to the alcohol occurs in the liver. MIBK is subject to conjugation with glucuronic acid prior to elimination in the urine (Lande et al., 1976) and it can also be eliminated unchanged in the urine (Zlatkis and Liebich, 1971). MIBK is a metabolic conversion product of 4-methylpentan-2-o1.

Toxicology

Inhalation of ketone vapors by humans is somewhat limited by the fact that they are irritating to the eyes and nose at relatively low concentrations. Sensory threshold studies indicate that the highest "satisfactory" exposure of MIBK to humans is 100 ppm (Nelson et al., 1943; Silverman et al., 1946). Inhalation of vapors can impair judgment (Rowe and Wolf, 1963). Nausea, headache and respiratory irritation have been found in workers exposed to MIBK at 100 ppm. Ketonic vapors cause narcosis with central nervous system depression. In a study of workers exposed to 500 ppm MIBK for 30 minutes daily, weakness, loss of appetite, headache, burning eyes, stomach ache, nausea, vomiting and sore throat were reported (NIOSH, 1978). Some of the workers had enlarged livers and colitis. Rats exposed to 200 ppm MIBK for 2 weeks had increased kidney and liver to body weight ratios (Schwuetz et al., 1974). Monkeys exposed at 100 ppm (hyperbarically) for 90 days had inflammation of the kidney. Rats exposed under the same conditions showed some degeneration and necrotic changes in the kidneys (MacEwen et al., 1971). No clear-cut evidence of neuropathy has been observed in humans or animals exposed to MIBK.

Effects of Concern

Mutagenicity

No studies of mutagenicity of MIBK have been found. Due to its high exposure, the Committee recommends that MIBK be tested for mutagenicity.

Teratogenicity

Due to the extremely high human exposure to MIBK and the indication of possible teratogenicity of the related aliphatic ketone, MEK (Schwetz et al., 1974), the Committee recommends that MIBK be tested for teratogenicity.

Chronic Effects

Subchronic toxicity of MIBK is well-characterized. However, long term toxic effects of MIBK have not been studied. Because of its extremely high exposure and the demonstrated subchronic effects the Committee recommends that chronic studies be performed to assess the effects of long-term exposure on laboratory animals.

Epidemiology

The long term toxic effects of MIBK have not been assessed, nor have epidemiologic studies been performed to determine chronic effects of MIBK exposure on humans. In light of its high level of exposure, the Committee recommends epidemiological studies.

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